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From puberty to menopause: Estrogen's role in migraine throughout women's lifespan

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ABSTRACT

Migraine is a neurological condition characterized by moderate to severe, unilateral throbbing head pain that affects more than one billion people worldwide. The incidence of migraine in prepubertal women and men has a similar prevalence, however during reproductive years, migraine is three times more common in women than in men of the same age. Recent studies have been highlighting the cause underlying this discrepancy is due to differences in sex hormone levels – particularly estrogen. Estrogen have been shown to increase serotonergic tone, promote the release of CGRP and nitric oxide, and modulate opioid pathway, which potentially playing a key role in migraine development.

Keywords: migraine, estrogen, menstruation, menopause

Abbreviations:

E1 : estrone
E2: estradiol
E3: estriol
Erα: estrogen receptor alpha
ERβ: estrogen receptor beta
GPER: G protein-coupled ER
GnRH: Gonadotrophin Releasing Hormone
FSH: Follicle Stimulating Hormone
LH: Luteinizing Hormone
GABA: Gamma-Aminobutyric Acid
hCG: Human Chorionic Gonadotropin
TCC: trigeminocervical complex
eNOS: endothelial nitric oxide synthase

INTRODUCTION

Migraine is a neurological disorder characterized by moderate to severe unilateral headaches. Migraine typically pulsating and exacerbated by routine activities such as walking and climbing stairs, which may also be accompanied by nausea, vomiting, photophobia and phonophobia. [1,2]. Despite being a non-life-threatening condition, migraine is the second most prevalent cause of disability worldwide [3].

Prior to puberty, the prevalence of migraine is approximately 4%, affecting both sexes equally. However, during reproductive years, women are three times more likely to develop migraine with higher pain intensity, longer attack durations, and higher risk for headache reoccurrence [4]. These significant sex-based discrepancy indicate that migraine are associated with sex hormone differences. In addition to epidemiological evidence of sex differences in migraine, change in migraine frequency and severity during menstruation, pregnancy, postpartum and menopause further implicates roles of hormones in migraine pathophysiology [5,6].

MIGRAINE PATHOPHYSIOLOGY

The trigeminovascular system consists of trigeminal nociceptive afferents that innervate meninges and peripheral intracranial blood vessels and trigeminocervical complex (TCC). This pain pathway is thought to be the generator of migraine. Activation of perivascular trigeminal afferents will lead to vasodilatation attributed to release of Calcitonin Gene-Related Peptide (CGRP) and substance P. These neuropeptides also act as a neurotransmitter to relay the migraine pain signal through the trigeminal ganglion to the TCC. From the TCC, pain will be projected ascendingly to various areas of higher structures and brain such as the hypothalamus, thalamus, and somatosensory cortex responsible for migraine perception [2,7-10].

While the pathophysiology of migraine is well-established to trigeminovascular system, evidence also highlights a significant role of hormonal factors—especially estrogen withdrawal—in modulating migraine susceptibility and severity [11]. Estrogen withdrawal hypothesis that stated that abrupt decline of estrogen shortly before menstruation may precipitate migraine attack was first described by Sommervile in 1972. This hypothesis emerged from an interventional study involving women with premenstrual and menstrual migraines, which demonstrated that estradiol valerate injection may delay the onset of menstrual migraine [12].

ESTROGEN

Estrogen is produced mainly by the ovaries, and in smaller amounts by adipocytes, liver, adrenal glands, and breasts [5,12]. There are three primary types of estrogen including estrone (E1), estradiol (E2), and estriol (E3) which have different predominant based on stage of female

reproduction. E2 is main hormone that is sustained over a woman's lifespan while E1 and E3 are weaker forms that become dominant during menopause and pregnancy, respectively [13].

The effects of estrogen on the brain may occur through passive diffusion of peripheral estrogen across the blood-brain barrier or synthesized in the brain from cholesterol [3, 14]. The actions of estrogen are mediated by the binding to estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G protein-coupled ER (GPER). These three receptors are found in the trigeminal ganglion, the caudal trigeminal nucleus, and hypothalamus which contribute to migraine pathophysiology [12].

MIGRAINE DURING MENSTRUATION CYCLE

Hypothalamic-hypophyseal-ovarian axis play important role in regulating woman's reproductive cycle [14]. In menstrual cycle, this pulsatile secretion of hormone will divide menstrual cycle into three stages including follicular phase, ovulation, and luteal phase. Hypothalamus will produce Gonadotrophin Releasing Hormone (GnRH) during follicular phase which will stimulates the anterior pituitary to secrete Follicle Stimulating Hormone (FSH), allowing up to 20 single follicles to grow. Approximately six days after the cycle begin, one follicle will grow faster while the other will regress. The developing follicle will produce estrogen, making negative feedback into pituitary gland to reduce FSH secretion and trigger Luteinizing Hormone (LH). Surge of LH will then cause rupture release of mature egg, known as ovulation [15].

The luteal phase begins right after ovulation. In this phase, the follicle has transformed into corpus luteum and will secrete progesterone and cause second rise of estrogen, stimulating the endometrium to prepare a thick layer of blood vessels for possible fertilization [14,15]. In the absence of fertilization, corpus luteum will degrade and the concentration of estrogen and progesterone will fall, causing menstrual bleed [15]. The concentration of estrogen is lowest during menstruation, will rise slowly during follicular phase, and peak the day before ovulation [12].

Throughout the reproductive cycle, the menstrual phase is the most significant phase for the occurrence of migraine attacks. Studies have shown that the likelihood of a migraine attack increases by 25% five days prior to menstruation, raised up to 71% two days before menstruation and reach 100% on the first day of menstruation [3]. This evident suggest that falling concentrations of estrogen in migraine pathophysiology as on those days concentration of estrogen is at its lowest [15].

Interaction between estrogen and migraine occurrence may occur through several mechanisms. Activation of estrogen receptors may increase serotonergic tone by increasing serotonin production, and decreasing serotonin reuptake and degradation. Serotonin has been

known to play a role in vasoconstriction of blood vessels in the brain, thus decreased serotonin levels due to decreased estrogen levels may lead to insufficient regulation of excessive cerebral vasodilation, thereby contributing to the development of migraines [13,16].

Estrogen may also affect the cerebral vasculature through activation of ERα, which stimulates endothelial nitric oxide synthase (eNOS) activity and increases the release of nitric oxide—a potent vasodilator. This, in turn, reinforces neurogenic inflammation and contributes to the throbbing and pulsating qualities of migraine headaches [3]. Moreover, central opioid tonus appears to be influenced by estrogen. During premenstrual period, plasma β endorphin which has analgesic and neuromodulator effects on peripheral and central pain seems to impaired. This opioid hyposensitivity may contribute to risk of menstrual migraine [17].

Estrogen's influence on migraine is closely linked to its effect on CGRP regulation. Estrogen receptors are highly expressed in CGRP-positive neurons in the trigeminovascular system. Animal study evidenced that deficiency of estrogen increases CGRP expression in various brain regions. Recent findings by Warfvinge et al. (2020) indicate that the decline in estrogen levels during menstruation is associated with elevated CGRP concentrations. Additionally, women suffering from migraine exhibited significantly higher plasma CGRP levels during menstruation compared to non-migraine female participants (5.95 pg/mL vs 4.61 pg/mL, $p = 0.020$) [18]. Furthermore, blocking CGRP signaling have been proven to be effective for acute and preventive treatment of migraine [12]. Animal study also demonstrated that reduced levels of estrogen were shown to increase the frequency of cortical spreading depressions, a wave of neuronal and glial depolarization followed by suppression of activity that moves across the cortex and is linked to migraines—especially migraine with aura. This probably because estrogen may rapidly alter cellular excitability and gene expression at hypothalamus [19].

In contrast with menstruation phase, the occurrence of migraine attacks decreases as progesterone levels increase during the luteal phase. Progesterone has been shown to have protective effect against migraine attacks by reducing activation of the trigeminal caudal nucleus, which leads to antinociceptive effects. In addition, the neurosteroid allopregnanolone, an active metabolite of progesterone, acts as a positive modulator of the Gamma-Aminobutyric Acid (GABA) receptor that possess antinociceptive effects and can prevent central sensitization [3].

MIGRAINE DURING PREGNANCY

Estrogen and progesterone level is increased in pregnancy. In early pregnancy, estrogen and progesterone is produced by corpus luteum as result of Human Chorionic Gonadotropin (hCG) stimulation. Once placenta was formed, the placenta will produce most of the estrogen and

progesterone necessary for pregnancy. Serum estradiol and progesterone levels begin to increase throughout pregnancy and reached peak level in the third trimester [14].

Most epidemiological studies have shown that the majority of women with pre-existing migraine report a remission in symptoms during pregnancy. Studies have found that approximately 50-80% of women experience a reduction in both the frequency and pain intensity of migraine attacks during pregnancy, particularly in the second and third trimesters. This improvement is likely attributed to the progressive increase in estradiol and progesterone levels during pregnancy, which are thought to play a neuroprotective role against migraine headaches [3,14].

In contrast to the improvements during pregnancy, migraine symptoms commonly reappear early during the postpartum period. Brandes 2006 reported 94% of patient reexperiencing migraine after delivery and this is thought to be related to sharply decline in estrogen levels following delivery [14,17].

MIGRAINE DURING MENOPAUSE PHASE

The transition from the reproductive phase to the non-reproductive phase caused by a decrease in the production of female hormones by the ovaries. This transition called the perimenopause period, characterized by significant fluctuations in estrogen and progesterone levels in the years leading up to menopause. During this transition, some women may experience worsening of migraine attack due to fluctuations in estrogen and progesterone levels [14]. The prevalence of migraine attacks decreases during the menopause period, as estrogen and progesterone levels are already stably low [17, 20].

CONCLUSION

The disparity in migraine prevalence between men and women, along with the fluctuation in migraine frequency and intensity during various reproductive milestones, suggests that migraine is influenced by sex hormones through their influence on cellular excitability and cerebral vasculature. With understanding that migraine attack influenced by sex hormone, especially estrogen, this may provide conceptual framework for further studies of possible association of estrogen with migraine.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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